

Division Director's Memorandum

NDA: 20-972

Drug and indication: efavirenz (SustivaTM) for treatment of HIV-1 infection

Dose: 600 mg orally once daily (as 50mg, 100mg and 200mg capsules)

Applicant: DuPont Pharmaceuticals Company

Submission dated: June 11, 1998

Date of Memorandum: September 16, 1998

In this application, the sponsor requests approval for efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. The primary source of evidence supporting the safety and efficacy of this drug is the results of three adequate and well-controlled clinical trials (DMP 266-006, DMP 266-020, and ACTG 364) conducted in 928 adults, and an uncontrolled open-label study (ACTG 382) conducted in 57 pediatric patients. The pivotal studies enrolled treatment-naïve and treatment experienced patients, however no data is provided for either protease inhibitor-experienced or NNRTI-experienced patients. Additional supportive information on safety and activity is provided by the results of phase I and phase II trials and the sponsor's expanded access program.

I concur with the recommendation of the review team that this application provides adequate information to support the safety and efficacy of this product and that accelerated approval should be granted. Several aspects of the database submitted in support of this approval merit comment and/or qualification:

1. Efficacy for this accelerated approval is principally based on analyses of surrogate marker data (including HIV RNA and CD4 cell counts) after 24 weeks of treatment with a regimen containing either efavirenz or a comparator. As noted in the clinical and biometrics reviews, interpretation of each of the three trials has a limitation that merits comment:

- a. Trial 006, conducted in patients naive to lamivudine, protease inhibitors and NNRTIs, provided for 24-week open-label comparisons between: (1) efavirenz and indinavir vs. indinavir, zidovudine and lamivudine, and (2) efavirenz, zidovudine and lamivudine vs. indinavir, zidovudine and lamivudine. Analyses of the proportion of patients with HIV RNA below the limit of quantification suggest that both efavirenz-containing regimens are comparable in efficacy to the comparator indinavir regimen. However, because the trial was open-label and because the rate of discontinuation was high (particularly in the indinavir group) no

conclusion about the sponsor's claim of superiority of the efavirenz, zidovudine and lamivudine group can be reached.

This trial illustrates an inherent problem with open-label trial designs. While this design minimizes the number of tablets that patients are required to take, interpretation of the results is problematic because of the potential for bias when treatment assignment is known.

The analytic problem of how to count patients with less than complete follow-up is particularly complicated in this trial by the high, but unbalanced drop-out rate. As noted in the group-leader memorandum, the rates of virologic response vary depending on how missing data are analyzed, but importantly, the overall conclusions remain unchanged. For purposes of labeling, the more conservative analysis (which assumes that discontinued patients were treatment nonresponders) will be reported.

b. Trial 020, conducted in nucleoside (NRTI)-experienced patients, provided for a blinded comparison between efavirenz, indinavir and NRTIs vs. indinavir and NRTIs. While at 24-weeks, a higher proportion of patients in the efavirenz group had an HIV RNA value below 400 copies than in the comparator group, this difference did not reach statistical significance. However, this lack of significance is somewhat less concerning because a significant difference between groups was found in two other analyses: (1) using the alternative ultrasensitive assay (which has yet to be validated), and (2) in a similar comparison in ACTG 364 (see below).

c. ACTG 364, conducted in heavily NRTI and clinical trial-experienced patients, provided for blinded comparisons between: (1) efavirenz, nelfinavir and 2 NRTIs vs. nelfinavir and 2 NRTIs (a similar comparison to trial 020), and (2) efavirenz and 2 NRTIs vs. nelfinavir and 2 NRTIs (a similar comparison to trial 006). In the first comparison, a higher proportion of patients in the efavirenz-containing regimen had an HIV RNA below the assay limits of quantification. In the secondary comparison, both regimens appeared to have comparable efficacy. These conclusions need to be qualified by several important factors: the highly select nature of the clinical trial participants, the preliminary nature of this analysis, and the fact that the trial remains ongoing with a planned analysis at 48 weeks.

Despite these qualifications, the available database suggests that during 24 weeks of therapy, the addition of efavirenz to a three-drug regimen containing a protease inhibitor provides benefit, and alternatively, a regimen containing efavirenz and two nucleoside analogues is comparable in efficacy to a three-drug protease inhibitor containing regimen. The sponsor's future submissions of results from ongoing trials 006 and 364 will be essential to evaluate whether these findings can be maintained during longer durations of treatment.

2. Safety is supported by data collected on 2215 persons. The primary safety concerns relate to CNS toxicity, rash, reproductive toxicity observed in primates, and the potential for drug interactions.

a. Mild and moderate CNS symptoms (including dizziness, headache, insomnia, depression, concentration impairment, agitation, abnormal dreaming, insomnia and others) were reported in approximately 50% of patients receiving efavirenz. More severe CNS symptoms (including severe depression, delusions, and seizures) were less frequently reported. In the majority of instances, CNS symptoms occurred within several weeks after initiation of therapy, improved with bedtime dosing, and resolved with continued therapy.

b. As has been observed with other members of the NNRTI-class, rash was observed in 27% of adults and in 40% of children. Rash was also more likely to be severe in children. Cases of severe rash (including Stevens-Johnson Syndrome) have been reported infrequently in both adults and children. Treatment needs to be discontinued in patients with these more severe manifestations.

The product labeling provides appropriate precautionary information about the incidence, predisposing factors and management of both CNS and dermal adverse experience.

c. Reproductive toxicity (anophthalmia, microphthalmia and cleft palate) was observed in the offspring of 3/20 primates dosed with efavirenz. Despite lack of replication in other species, this finding is of particular concern because: the study was conducted in primates, the exposure was similar to human exposure at the 600mg daily dose, efavirenz has been shown to penetrate the CSF, and the structural abnormalities were severe and appeared related. No human data are currently available.

The label will provide a warning that describes the animal findings, advises that pregnancy be avoided in women using this product, and advises that women undergo pregnancy testing prior to initiation of therapy. Similarly, the label will recommend that this product only be used in pregnant women in whom the benefit outweighs the potential risk (such as those who lack other therapeutic options). To provide further information on this issue, the sponsor has committed to t(b)(4)(CC)-----

d. The sponsor has provided an extensive database evaluating the potential for drug interactions between efavirenz and drugs likely to be coadministered or to interact with it. As provided in tabular and narrative form in the product label, the clinician needs to be aware of the potential for interactions (in several possible directions) between efavirenz and other drugs that (like efavirenz) either induce or are substrates of CYP3A4 and other isoenzymes.

3. Sustained viral suppression (i.e., viral suppression beyond 24 weeks of treatment) has not been established for efavirenz. Accordingly, this application will be approved under the Subpart H regulations for accelerated approval and results after 48-weeks of treatment from ongoing studies 006 and ACTG 364 will be submitted to support traditional approval.

4. Several issues remain incompletely addressed by this application. To provide further

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The review team for efavirenz should be commended for their thorough and expedited review of this complex new drug application that provides for an important new therapeutic option for patients with HIV-infection.

There are no outstanding regulatory issues.

Heidi M. Jolson, M.D., M.P.H.
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